UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ASTELLAS INSTITUTE FOR REGENERATIVE MEDICINE, Plaintiff, v. IMSTEM BIOTECHNOLOGY, INC., XIAOFANG WANG, and REN-HE XU, Defendants.	C.A. No. 1:17-cv-12239

DEFENDANTS' POST-TRIAL
PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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INTRODUCTION

This lawsuit arises from a once-amicable scientific collaboration between two of Plaintiff's scientists (Drs. Kimbrel and Lanza) and two Defendant scientists (Drs. Wang and Xu) concerning protocols for making, and methods of using, human mesenchymal stem cells ("MSCs").

The gravamen of the case is about giving credit where credit is due, *i.e.* crediting *all* of the inventors of the disputed patent claims. Drs. Kimbrel and Lanza brought to the parties' collaboration a basic, low-yield, four-step recipe for differentiating human embryonic stem cells into cells that might (or might not) be MSCs. The recipe was itself built on others' work (some credited, some not). Drs. Wang and Xu proposed a novel use for the cells – to treat multiple sclerosis – and then made improvements to the recipe that increased yield, utility, safety, and therapeutic efficacy. Their effort, expertise, insight, and contributions warrant acknowledgment.

Plaintiff's ancillary state law claim – which has served primarily as a vehicle for casting aspersions at trial – is without merit. Beyond bruising egos, the parties' failure to name each other on their patents has not caused anyone any actual harm. Plaintiff admits as much. Its attempt to nevertheless capture ImStem's "implied value" is untethered to the facts or the law.

PROCEDURAL BACKGROUND

Plaintiff Astellas Institute for Regenerative Medicine ("Astellas") filed this action against Defendants ImStem Biotechnology, Inc. ("ImStem"), Dr. Xiaofang Wang ("Dr. Wang"), and Dr. Ren-He Xu ("Dr. Xu") (collectively, "Defendants"), asserting claims for correction of inventorship of a patent per 35 U.S.C. § 256 (Count I – sole inventorship; Count II – joint inventorship), conversion (Count III), unjust enrichment (Count IV), unfair trade practices under Massachusetts General Laws Chapter 93A (Count V), trade secret misappropriation (Count VI),

negligent misrepresentation (Count VII). (ECF 1).[1] Defendants filed counterclaims for correction of inventorship of two rival patents and for unjust enrichment. (ECF 91). Two years into the case, Astellas added a breach of contract claim (Count VII) (ECF 96, 113).

The claims then narrowed. The Court granted partial summary judgment as to Count II, determining that Drs. Kimbrel and Lanza should be added to the '551 patent.[2] (ECF 127, 163). Plaintiff then dropped Counts VI, VII and VIII at the pre-trial conference, and Counts III and IV on the eve of trial.[3] Defendants dropped their unjust enrichment counterclaim.

Accordingly, the case was tried as to Plaintiff's Count I (sole inventorship of the '551 patent) and Count V (c. 93A) and Defendants' Counterclaim Count I (joint inventorship of the '956 patent[4]) and Counterclaim Count II (joint inventorship of the '321 patent[5]).

FINDINGS OF FACT

I. Facts Relevant to the Inventorship Claims

A. The Parties

1. Astellas is a U.S. affiliate of Astellas Pharma Inc., a pharmaceutical company based in Tokyo, Japan. Plaintiff's principal place of business is 33 Locke Drive, Marlborough, MA 01752. Tr. 1-78:23 to 1-79: 2; *see also* ECF 220-1 (Ex. A) at ¶ 1.

2. ImStem is a corporation organized and existing under the laws of Connecticut and its principal place of business at 400 Farmington Ave., R1808, Farmington, Connecticut 06030.

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[1] The original Complaint included co-plaintiff Stem Cell & Regenerative Medicine International, Inc. ("SCRMI"). SCRMI was a joint venture between Astellas' predecessor ACT and a South Korean company. ACT was eventually acquired by Astellas, which later also acquired co-Plaintiff SCRMI and any/all of its claims in this case. The names SCRMI, ACT, and Astellas are therefore interchangeable unless otherwise noted.

[2] U.S. Patent No. 9,745,551.

[3] Plaintiff was responding to the Court's recent holding in *Mack v. Cultural Care Inc.*, Civ. No. 1:19-cv-11530-ADB, 2020 WL 4673522, at *9 (D. Mass. Aug. 12, 2020), quoting *Shaulis v. Nordstrom, Inc.*, 865 F.3d 1 (1st Cir. 2017) ("First Circuit has recently clarified that a 'common law claim for unjust enrichment . . . fails because a party with an adequate remedy at law cannot claim unjust enrichment.").

[4] U.S. Patent No. 8,961,956.

[5] U.S. Patent No. 8,962,321.

ECF 113 ¶ 12; ECF 114 ¶ 12.

3. Dr. Xu is a Professor and Associate Dean at the University of Macau. During the relevant time period, he was an Associate Professor at the University of Connecticut ("UConn"), Director of its Stem Cell Institute, and co-founder and former Chief Scientific Officer of ImStem. Tr. 10-17:25 to 10-19:8; *see also* 10-130:1-4.

4. Dr. Wang is a co-founder and employee of ImStem and lives and works in Connecticut. Tr. 6-9:25 to 6-10:20.

B. Background Science as of 2009

5. The instant action concerns human stem cell development and differentiation.

6. In nature, when an egg is fertilized by a sperm, the fertilized egg begins a process of division. The first cell splits into two cells, the two become four, the four become eight, and so on. At some point, these first "undifferentiated" (*i.e.* functionally identical) human embryonic stem cells ("hESCs") begin to differentiate; *i.e.* to express different genes and distinguish themselves into cell types that will eventually give rise to the full range of cells in the human body: bone, cartilage, nerves, skin, blood cells, organs, and tissues of all sorts. Tr. 8-17:22 to 8-19:8.

7. Mesenchymal stem cells ("MSCs") are quasi-differentiated cells that have the ability to become a wide range of bodily cells, such as bone, fat, and cartilage. While less pluripotent than precursor hESCs, they retain the ability to change and develop into a wide range of cell types. Tr. 6-30:7-14.; *see* Tr. 7-34:24 to 7-46:20.

8. MSCs occur in nature but they are transient. By 2009, scientists had attempted to reproduce them in the laboratory but the exact mechanisms and processes of natural MSC formation and differentiation was not fully understood. Tr. 6-22:16 to 6-23:5.

9. As of 2009, scientists were still coming to terms with what exactly constituted a

true, laboratory-made "MSC." Much about stem cell differentiation and the underlying biological mechanisms was poorly understood. Tr. 6-31:15-6-32:1.[6] Much of it remains a mystery today. Tr. 6-22:16 to 6-23:5.

10. At the time, there were several known methods of obtaining or manufacturing MSC-like cells. Scientists had developed recipes for taking cells from fat, bone, placenta, and other cells and coaxing them – through a series of chemical stimulants in the laboratory – into becoming MSC-like cells. Each of the resulting kind of "MSCs" were different and had different properties. Tr. 6-32:13-25; Tr. 7-38:15-7-39:3.

11. While there was scientific interest in how these cells might be used therapeutically, the vast majority of the work done by late 2009 was *in vitro* (*i.e.* in the lab) not *in vivo* (*i.e.* in an animal) and directed to a range of conditions not at issue in this case. *See generally* Tr. 7-14:21 to 7-44:24; Tr. 6-29:2-19; Tr. 6-38:8-18; Tr. 6-70:8-17; Tr. 6-73:1-6.

C. The Defendants in 2009-2010

12. In 2009, Dr. Xu was a prominent, globally-trained stem cell scientist in the field of human embryonic stem cells. He had earned a medical degree in China, Tr. 10-6:21-22, worked as a researcher in China, Israel, and at NIH in Bethesda, MD, Tr. 10-7:10 to 10-8:15, and obtained his Ph.D. at the University of Tokyo in embryo genetics, Tr. 10-9:6-8.

13. Dr. Xu had been the first employee and the senior scientist of WiCell, the University of Wisconsin laboratory where the first human embryonic stem cell had been isolated in 1999. Tr. 10-9:19 to 10-10:21; Tr. 10-11:11-17. Dr. Xu had been recruited by the founder of WiCell, Dr. James Thomson. Tr. 10-11:5-10.

14. Dr. Xu had been the first scientist to differentiate human embryonic stem cells

[6] The science is still controversial today. Some scientists have since contested the value of the "MSC" moniker and called for its abandonment in light of the variability and unpredictability of the cells. TX-WJ.

(hESCs) into trophoblasts using a molecule called BMP4, a process he had published in Nature Biotechnology in 2002 and for which he had obtained a patent in 2004. Tr.10-12:14 to 10-14:4; TX-TO.

15. By 2009, Dr. Xu was Associate Professor at the University of Connecticut Health Center. He was also the Director of its Stem Cell Institute (having previously been recruited by several states[7]) and on his way to training over 100 scientists in stem cell development and differentiation. *See* Tr. 10-17:25 to 10-19:8; *see also* Tr. 10-130:1-4.

16. Dr. Xu had been recognized by the State of Connecticut for his research and leadership. Tr. 10-23:2-17. He was a published and recognized leader in the field.

17. Dr. Wang was his post-doctoral researcher and a promising scientist in his own right. Tr. 10-25:18 to 10-26:4. Dr. Wang had graduated from an elite MD/MS program at Peking University and received his Ph.D. in Immunology from the University of Texas Health Science Center at Houston/MD Anderson Cancer Center. Prior to joining Dr. Xu's lab, he had focused for some time on the field of immunology. Tr. 6-12:5 to 6-19:6.

18. Dr. Wang spent that last two years of his doctoral program studying at Yale. Tr. 6-17:17-21. While at Yale, Dr. Wang had developed expertise in a particular mouse "model" ("EAE"), a carefully engineered mouse designed to mimic multiple sclerosis for purposes of drug testing and analysis.[8] Tr. 6-40:24 to 6-41:4. The EAE model is a difficult model to build and master. Tr. 6-44:17 to 6-45:2; Tr. 7-53:8-21.

19. After Yale, Dr. Wang joined Dr. Xu's lab. Early in his tenure there, he made a

[7] After the Bush Administration denied federal funding for research on human embryonic stem cells, many states began their own research programs funded with state monies. Dr. Xu was recruited by several states to lead their human embryonic stem cell research programs.

[8] ImStem's expert, Dr. Bunnell, explained that it took him 18 months to master the construction of the model. Tr. 7-50:6-8.

significant discovery regarding a protein named beta FGF for which he won an award. Tr. 6-18:15 to 6-19:6.

20. By early 2010, Dr. Wang was working in Dr. Xu's laboratory on cell adhesions, how to differentiate certain types of neuron cells, and cell signaling pathways of embryonic (ES) cells. Tr. 6-24:4-10.

21. At Dr. Xu's request he also wrote an academic book chapter on stem cell differentiation, MSCs, and the possibility of using hESC-derived MSCs to treat multiple sclerosis, something that had not yet been tried. Tr. 6-25:23 to 6-29:15; *see* TX-BW; TX-FD. The book chapter represented Drs. Xu's and Wang's assessment of both the state of the art and, significantly, their ideas as to where it might go. Tr. 6-29:2-15.

D. The Plaintiff in 2009-2010

22. In late 2009, Astellas' predecessor-interest (ACT) was a small, cash-strapped start-up exploring a variety of life-science technologies. *See* Tr. 1-79; 11-20; *see also* Tr. 1-90:9-25; Tr. 1-95:19 to 1-96:9.

23. Three Astellas employees (Erin Kimbrel, Shi-Jiang Lu, and Robert Lanza) developed a protocol – essentially a recipe – for making a new kind of MSC-like cell. [9]

24. The protocol was built upon an earlier paper that Drs. Lu and Lanza had published describing a process for starting with hESCs and differentiating them (using chemical stimulants) into cells called "embryoid bodies," then differentiating the embryoid bodies into cells called "hemangioblasts." Tr. 1-97:9-20. Now, in late 2009, Drs. Lu, Kimbrel, and Lanza added a fourth step to the recipe, further differentiating the hemangioblasts into MSCs, or so-

[9] Drs. Lu and Kimbrel worked at SCRMI, which was a joint venture between ACT and a South Korean company. *See* Tr. 1-79:11 to 1-80:12; Tr. 1-97:19 to 1-98:1; Tr. 1-103:10-15. Dr. Lanza was employed by ACT but oversaw Dr. Kimbrel's work at the SCRMI joint venture. Tr. 1-89:15-21; Tr. 1-103:7-19. ACT was later renamed Ocata Pharmaceuticals and then acquired by Astellas, which later also acquired the balance of SCRMI. Tr. 1-80:1-12.

called "hemangioblast-derived MSCs" or "HB-MSCs." Tr. 2-19:19-21.

25. At least one other scientist, Dr. Slukvin of the University of Wisconsin, had already independently derived MSCs from hemangioblasts. Tr. 10-27:3-6; 10-51:2-7.

26. Dr. Kimbrel succeeded in adding the fourth step to the Lu recipe and obtained cells that had some of the chemical signatures/protein expressions of MSCs. Tr. 2-31:8-11. Critically, however: (i) Kimbrel and Lanza did not know whether the cells were true MSCs (a controversial label even if asserted) because they lacked the skills and infrastructure to test their new cells *in vivo*, Tr. 2-94:17-21; (ii) they had not fully investigated the full range of secretions that might (and eventually did) play an important role in *in vivo* functionality, Tr.2-98:7-12; and (iii) they had not yet fully conceived of all of the therapeutic uses of the cells. Tr. 2-94:22 to 2-95:19.

27. Dr. Lanza's contribution to the recipe – and his only allegedly corroborating evidence at trial – was one email posing one question and attaching a promotional article regarding a different cell.[10] Dr. Lanza wrote: "Any *chance* we *might* be able to isolate ESC-derived cells with similar characteristics/immunomodulatory properties?" TX-38 (emphasis added).

28. There is no other contemporaneous documentary evidence indicating Astellas' interest in multiple sclerosis as a particular target.

29. In early 2010, Dr. Kimbrel froze the cells, put them in storage, and turned her attention to other projects. Tr. 2-91:20 ("I sort of shifted [my] focus [to other cells]"); Tr. 2-32:9-16 ("I was just keeping them so that we could, you know, take them back out when we had more time and plans."). No one at ACT had called out multiple sclerosis as a potential target.

[10] When asked his reaction to this assertion, Dr. Xu testified: "I just laughed." Tr. 10-33:18.

Tr. 2-95:1-2. No one did anything to test the cells against multiple sclerosis. *Id.;* Tr. 2-32:9-16.

30. Nearly half a year later, in June 2010, the cells were still frozen. Tr.2-94:10-15.

E. First Meetings and "Multiple Sclerosis" Invention

31. In June 2010, Dr. Lu encountered Dr. Xu at a conference in San Francisco. Tr. 10-29:21 to 10:30:18. Dr. Xu introduced his new post-doc, Dr. Wang, to Dr. Lu. *Id.*

32. Dr. Xu told Dr. Lu that he and Dr. Wang had recently been thinking about the therapeutic uses of stem cells, including differentiated stem cells. Tr. 10-30:7-11. Dr. Lu responded that his company ACT had a new cell type that might be of interest. Drs. Xu and Wang proposed a collaboration. *Id.*; Tr. 6-40:14-19. [11] The cells were brand new, unknown; Xu and Wang suggested that perhaps they could be therapeutically effective against multiple sclerosis. *Id.*

33. This was the first concrete mention of – and directed focus upon – multiple sclerosis in the collaboration. Tr. 10-31:14-21. To that point, Dr. Kimbrel had done nothing with respect to multiple sclerosis, Tr. 2-95:12 to 2-96:5, and indeed no one in the field had tested hESC-derived MSCs of any type against multiple sclerosis *in vivo*. Tr. 10-31:22-25.[12] Dr. Lu responded positively.

34. Indeed, it was Drs. Xu and Wang's intervention that revived ACT's HB-MSC program. Tr. 2-92:14 to 2-93:15.

35. The parties decided to have a follow–up meeting in Marlborough, MA at ACT's facilities. On July 13, 2010 the three met and Drs. Xu and Wang asked follow-up questions about who was working on the new cells. Tr. 6-39:7 -24; TX-16. The three scientists solidified

[11] Neither party produced Dr. Lu and both parties acknowledged that Drs. Lu, Xu, and Wang were the only three participants at the meeting where the collaboration was conceived.

[12] The prior art to which Dr. Fortier pointed at trial related to other kinds of MSCs, and only safety. Tr. 6-98:15-25.

their plans and the concept of using these new cells to treat multiple sclerosis. Tr. 6-40:14-19.

36. After these initial meetings, Dr. Lu reported back to ACT and through a series of emails introduced Dr. Kimbrel to Drs. Xu and Wang. TX-16. These emails corroborate both the existence and the substance of the meeting.

37. Dr. Kimbrel's first emails with Dr. Wang were revealing. On July 29, 2010 she wrote: "I am not familiar with the EAE mouse model and am curious as to your thoughts on how you would use these cells in a model for autoimmune disease." TX-11. This email and others underscored Dr. Kimbrel's relative unfamiliarity with multiple sclerosis (for which the EAE model was a widely used model) and the degree to which Drs. Wang and Xu were contributing to the early conversations.

F. Collaborators, Not Lab Technicians

38. From the outset, Drs. Lu, Kimbrel, Xu, and Wang understood the parties were forming a true "collaboration" – a term the parties used throughout correspondence and at trial. Drs. Xu and Wang were not merely lab technicians running routine tests at the direction of ACT. Rather, the parties understood Drs. Xu and Wang would be implementing and working with the recipe themselves, examining the cells, and investigating the underlying science. *See generally* Tr. 1-93:3-25; 1-180:16-25; 10-34:6 to 10-35:1.

39. Defendants did not need the ACT cells for any other purpose; they had access to other MSCs since UConn had other scientists working in this field. Tr. 10-35:10-11.

40. Nor were they to be paid by ACT/Astellas. Tr. 1-182:3-13; Tr. 3-204:7-9. Rather, the allure of this collaboration was the prospect of discovering new science and publishing a joint paper, a point on which the parties quickly agreed. Tr. 1-182:3-13; Tr. 10-79:10-18.

G. The GSK3i Recipe Improvement and Invention

41. Over the next several weeks, Wang and Xu met with Kimbrel, obtained some

samples of the purported "MSCs," designed a testing protocol, and began testing the cells.[13] Tr. 6-155:17 to 6-156:6. Wang and Xu started sharing their results (and ideas) with Kimbrel and Lanza. *See, e.g.*, TX-NB; TX-SI; TX-DS; TX-EW. The parties were in regular contact. *See, e.g.*, TX-17, TX-22.

42. As the experiments continued, the parties agreed that Dr. Wang should make the HB-MSCs himself, in-house, using the four-step hESC-EB-HB-MSC protocol that Dr. Kimbrel had given him. Tr. 10-36:9-21. Dr. Xu's lab had access to and experience with multiple cell lines, whereas ACT had just one. Tr. 10-36:10-14; Tr. 10:43:14-20. For paper publication purposes, the parties wanted to test the protocol using multiple cell lines. *Id.*

43. Dr. Kimbrel had used a "feeder" system to culture the hESC's in the first stage of the recipe. Tr. 2-84:1-8. That is, the stem cells were grown on a bed of mouse or human cells that provided certain growth factors for the growing human embryonic stem cells but also polluted them (with mouse or non-self materials), making the downstream MSCs less suitable for human trials and FDA approval. Tr. 2-103:20-24; Tr. 6-55:11 to 6-56:15; Tr. 8-48:14-18.

44. Wang decided to switch to a "feeder-free" system in which the initial hESCs would be grown without mouse feeder cells. Tr. 6-54:8 to 6-55:10. When that switch to a feeder-free starting point lowered the recipe's yield – producing failed batches, poor-quality EBs, poor-quality HBs, and few final cells – Wang and Xu set about improving the recipe in order to advance the collaboration. *Id.;* Tr. 10-36:18 to 10-37:19.

45. Drawing upon his own experience, Wang came up with the idea of adding a new chemical, 6-bromoindirubin-30-oxime (BIO) ("GSK3 inhibitor" or "GSK3i"), at a specific

[13] For expedience, Xu and Wang initially worked with another laboratory which performed the testing at their direction, since that laboratory had the necessary permits. Tr. 3-26:2-7. Once Xu and Wang got the necessary permits for conducting the tests with EAE model themselves, they did so. Tr. 3-26:8-10; Tr. 10-57:1-18.

concentration, to the initial culturing medium in which the hESCs were grown. Tr. 6-55:8-10.

46. GSK3i had never been used in this kind of four-step recipe. *See* Tr. 8-43:15-22; *see also* Tr. 8-154:21-24; TX-40F. Moreover, Wang was using it in an unexpected way. Whereas the prior art had taught using a 1-2 µM dose of GSK3i to *prevent* differentiation and thus preserve hESCs in an undifferentiated state, Wang theorized and determined that a lower dose (0.2µM) might actually *promote* differentiation in the later stages of a multi-stage recipe like this one.[14] *See* Tr. 6-65:5-11; *see also* Tr. 6-67:5-10; Tr. 8-125:4

47. As Defendants' expert (Dr. Perry) explained at trial, GSK3i affects the powerful "Wnt signaling" system of chemical communications that governs cell differentiation and affects downstream cell fate, Tr. 8-22:23 to 8-24:21, precisely the opposite of the effect memorialized in prior art articles such as Dr. Brivanlou's 2004 paper on the subject. Tr. 8-124:4 to 8:125:15.

48. Dr. Wang recorded his findings in his lab notebook, TX-BT, and reported his findings to his lab colleagues. *See* TX-X.

49. The Xu/Wang revised protocol yielded better, more defined and tightly-ordered clusters of cells in the second (EB) step, and greater yield in the third (HB) and fourth (MSC) steps. Tr. 6-66:4-25. Wang and Xu's use of GSK3i improved both quality and quantity, critical for use in a real-world clinical setting.

50. The Court accepts Dr. Perry's testimony that GSK3i had unpredictable and surprisingly beneficial downstream consequences. Tr. 8-36:18 to 8-37:24; Tr. 8-42:15-25.

51. Astellas' expert (Dr. Brivanlou) acknowledged he was an expert only in the first stage of the four-stage recipe, Tr.4-74:1-13; Tr.4-80:1-24, and comparatively unfamiliar with "downstream" differentiation in this case. Tr. 4-22:1-25; 4-22 4-69:6-14; 4-80:1-7 ("way too late

[14] Indeed, Dr. Wang found that the concentration taught by Plaintiff's expert (Dr. Brivanlou) actually killed the cells in this particular setting. Tr. 6-64:7-8; *see* TX-X at 21.

for me"). When confronted with his deposition testimony, he conceded that (i) he did not know if GSK3i affected HB differentiation, downstream of EB's, Tr. 4-84:5-12; 4-85:20-25; 4-86:20-24 ("I cannot tell you if GSK3 inhibitor is going to show up downstream of the EB's"); that (ii) stem cells can differentiate in unpredictable ways, Tr. 4-87:8-19; and that (iii) Wnt signaling in particular is complicated and not fully understood. Tr. 4-96:6-17.

52. The Court concludes that Dr. Perry's more nuanced analysis of the downstream effects of GSK3i provides a more complete picture of the impact of using GSK3i in the protocol.

H. The Mitotic Inactivation Improvement and Invention

53. Drawing upon their book chapter and their own expertise, Drs. Xu and Wang also came up with the idea of "mitotically inactivating" the new cells after they had been formed. As they knew from their book chapter, the notion had only been explored *in vitro*, Tr. 6-29:2-19, Tr. 6-101:16 to 6-102:18, and only in other kinds of cells for other diseases (not MS). *Id.*; Tr. 6-38:8-18; Tr. 6-70:8-17; Tr. 6-73:1-6.

54. Behavior *in vitro* was not always predictive of behavior *in vivo*. Tr. 7-42:2-3; Tr. 6-102:6-18. The Court credits Dr. Bunnell's testimony that scientists did not thoroughly understand how MSCs imparted therapeutic effect. Tr. 7-42:4 to 7-44:17. It was believed that the emissions of various protein "factors" from the cells might play a role, *id*., but the mechanics of that process were unknown. *Id.*

55. Even the basic question of what the cells were emitting and how those emissions interacted with each other was not well understood. Tr. 7-43:22 to 7-44:14.

56. No one knew whether mitotic inactivation would affect cell DNA, other processes, cell marker expression, or therapeutic effect. Tr. 6-37:12 to Tr. 6-38:7.

57. No one knew how mitotic inactivation would affect cell mobility, longevity, function, efficacy, toxicity, cell-to-cell communication, for these cells, for this disease, *in vivo*.

Tr. 6-72:8-20; Tr. 6-73:1-6; Tr. 6-74:21-24.

58. This particular "witches brew" of chemicals, Tr. 7-31:20, could affect how the MSCs would move in the body, function, pass, aggregate, clot, talk to each other – none of which was known at the time. Tr. 7-42:12-23; Tr. 6-37:12 to Tr. 6-38:7; Tr. 6-72:8-20.

59. Drs. Wang and Xu nevertheless theorized that *these* new cells might still emit signature chemicals in a beneficial way and that mitotic inactivation might not interrupt the foregoing complex *in vivo* functions, Tr. 6-37:6 to 6-38:23; the inactivated cells would retain function, longevity, cell-to-cell communications, etc. in a manner that would leave intact their beneficial effect while removing the risk of tumors. *Id;* Tr. 7-63:2 to 7-68:2. Drs. Xu and Wang theorized the MSCs might have therapeutic use *in vivo* even if the MSCs were unable to subdivide (the ordinary behavior of MSCs) because they would nevertheless continue to secrete beneficial cytokines during their lifespan while still functioning. Tr. 7-65:20-22; Tr. 7-68:21.

60. At trial, Plaintiff's expert (Dr. Brivanlou) affirmed his prior deposition testimony – a four-page soliloquy in which he declared the idea of mitotically inactivating these cells to be "novel," "an innovation," and "an invention" – and thus confirmed his opinion that the idea of mitotically inactivating HB-MSCs was novel and an invention. Tr. 4-105:1 to 4-106:18.

61. Although Dr. Brivanlou was not designated to offer an opinion with respect to this issue, the length of his answer at deposition and the fact that he, a stem-cell scientist for decades, "ha[d] not seen it before," Tr. 4-106:15-18, has evidentiary value.[15]

62. Drs. Xu and Wang memorialized their invention in a UConn grant application by which they sought funding for the collaboration. Tr. 6-53:12-13; Tr. 10-204:1-3. Dr. Wang wrote the first draft in December 2010. TX-AD at 2 (Aim 3: to determine whether "irradiated

[15] Astellas proffered Dr. Brivanlou as an expert in, among other things, in "human embryonic stem cell derivation and differentiation and culturing techniques," and not simply GSK3i. Tr. 4-17:14-21.

[*i.e.* mitotically inactivated]" cells would work as well as live ones). Dr. Xu cleaned up Dr. Wang's prose in the final draft, which he forwarded to ACT on January 14, 2011, thanking them for their "passion for our ongoing and future collaborations." TX-CC at 1.

63. No one from ACT indicated that the idea was obvious, nor is there any record of UConn having responded that the idea was obvious or already known.

64. The Court does not credit Dr. Fortier's testimony to the contrary. Dr. Fortier, a veterinarian, demonstrated less command of the relevant science than Dr. Bunnell. In particular, Dr. Fortier had never worked with the EAE mouse model at issue and had no experience studying or treating multiple sclerosis. Tr. 3-130:10-15.

I. The BM-MSC Potency Improvement and Invention

65. In the fall of 2010, again drawing upon their book chapter, Wang and Xu conceived of the idea of comparing the immunological potency of the new HB-MSC cells to an MSC created using another, older recipe (so-called bone-marrow-derived MSCs or "BM-MSCs"). *See generally* Tr. 6-34: 3-24; TX-FD. Their focus was on therapeutic potency, not just numbers or lab notes on a page.

66. The notion of undertaking a potency assay arose from Drs. Wang and Xu's notion of using the cells to regulate the immune system. Tr. 6-82:1-6. Tr. 7-74:1-5; *see, e.g.*, Tr. 6-34:10-23. It would allow the collaboration (and practitioners thereafter) to identify cells for therapeutic use. Tr. 7-73:25 to 7-74:3. Potency may be donor dependent, age dependent, sex dependent, possibly race dependent, toxin exposure, and media dependent. Tr. 6-33:18-24.

67. The Court credits Dr. Bunnell's testimony that the idea of undertaking a comparison with BM-MSCs, while more modest conceptually than the other contributions, was not insubstantial. Tr. 7-73:25 to 7-74:15; TX-9 (in title of joint paper).

68. As with the mitotic inactivation invention, Drs. Wang and Xu memorialized their

BM-MSC potency comparison idea in the January 2011 UConn grant application to raise money for the collaboration, which they shared with Drs. Lu and Kimbrel. TX-AD (Dec. 2010 draft) at 2 (Aim 1); TX-CC at 1.

69. Neither ACT nor UConn indicated at the time that this idea was obvious or was not novel.

J. The IL-6 Screening Improvement and Invention

70. As the collaboration continued, Wang and Xu also identified a key feature of the new cells. MSCs were known to produce and express a myriad (100s to 1000s) of organic compounds ("factors") that each potentially played a role in therapeutic outcomes. *See* Tr. 6-88:4-7.

71. In June 2012, Dr. Wang ran a broad-spectrum genetic screening tool, "RNA Micro Array," against the new cells and noticed. Tr. 6-81:8-14; TX-BU at 25. Some of the cells secreted low levels of a particular factor called interleukin-6 or "IL-6," a chemical that Dr. Wang recognized (based on his expertise in autoimmune diseases) was associated with immune system regulation. Tr. 6-78:13-15; TX-BU at 25 (lab notebook).

72. Critically, Dr. Wang not only spotted the 1000-fold difference, he theorized that the low IL-6 might be relevant to the new cells' therapeutic function for multiple sclerosis. Tr. 6-81:5 to 6-84:11.

73. IL-6 can function in both a pro- and anti-inflammatory manner in different contexts. *See* Tr. Tr. 7-60:14 to 7-61:14; Tr. 7-77:1-8; Tr. 6-79:12 to 6-80:11.

74. Dr. Wang's theory ran counter to the conventional wisdom. At the time, *high* IL-6 was thought to be necessary or beneficial to therapeutic effect. Tr. 6-80:8-11; Tr. 7-76:20-24. Some scientists had even gone so far as to shut down IL-6 secretion and found the MSCs to lose all therapeutic function, further reinforcing the belief that IL-6 was necessary. Tr. 6-81:1-4.

75. Dr. Wang nonetheless contacted Dr. Xu, discussed his findings and theory, and developed a test to examine the low IL-6 effect – taking into account the possibility that conventional BM-MSCs may have had their naturally high levels of IL-6 inadvertently suppressed, Tr. 6-82:18-6:84:6, and determined that low IL-6 was driving therapeutic effect. Low IL-6 cells were better therapeutically. Tr. 10-100:4-14.

76. Significantly, IL-6 expression at a low level is not a fixed, inherent feature of the new cells. Some cells produced higher IL-6, some lower. Tr. 10-163:25 to 10-164:2.

77. Further, a single protocol can yield different batches of cells when run, and those batches can differ from one another. Tr. 2-105:23 to 2-106:4.

78. Further, even a single batch of HB-MSCs can change over time. As the cells aged or went through more "passages" from plate to plate, IL-6 levels increased and the cells became less therapeutically effective. *See* Tr. 10-233:12-23.

79. The Court finds, therefore, that Dr. Wang was not merely looking at a fixed/inherent feature of all HB-MSCs but instead establishing a criterion for future selection among batches, cells, and passages.

80. On November 5, 2011, Dr. Wang described his idea and research to Dr. Kimbrel, specifically calling out his interest in the "anti-EAE" therapeutic effect, and designing further experiments to "enhance the effect." Tr. 6-90:11-6-91:7; TX-PH. As with their other insights and contributions to the collaboration, Dr. Wang was focused on therapeutic effect, and on making the recipe and the cells better suited to real-world treatment of multiple sclerosis. *Id.*

81. Rather than just taking a measurement and writing them down, Drs. Wang and Xu went further, developed a hypothesis, a concept, an invention and then reduced it to practice.

82. The contrast with Kimbrel at the time was striking.[16] In early 2012, Dr. Kimbrel ordered and ran a "custom antibody array" that measured about 20 secretions. TX-43. It was a garden-variety battery of tests and Kimbrel treated it as such. *See* Tr. 7-78:6-25; *see also* Tr. 2-73:8-16; TX-43. In her March 2012 presentation to her colleagues, she did not circle or highlight the IL-6 data. TX-43. Indeed, she shelved the data without further analysis or – it appears – comprehension.

83. Even in January 2013, almost a year after running her micro-array and months after Wang's email, Kimbrel still did not quite realize the significance of Dr. Wang's work. In response to Dr. Wang's proposal for a conference presentation highlighting his work with IL-6, she wrote: "I have only a little bit of data on IL-6, it may complement yours but haven't followed up on it. . . . no one here is following up on IL6 either . . . ." TX-RP.

84. Simply put, Kimbrel had collected "a little data" about IL-6 and put it on the shelf for a year. Wang, by contrast was running a sophisticated genetic test, analyzing IL-6, testing therapeutic effect of low IL-6. He did this despite the conventional wisdom – uncontested at trial – that the best cells were thought to have high IL-6. Kimbrel did not know what she had, and she never asked anyone to measure therapeutic effect.

85. The Court does not credit Dr. Fortier's testimony to the contrary. Dr. Fortier again demonstrated less command of the relevant science than Dr. Bunnell. In particular, Dr. Fortier has no experience studying or treating multiple sclerosis. Tr. 3-130:10-15.

K. Common Theme: Moving the Recipe from Benchtop to Bedside.

86. All of Xu and Wang's contributions to the collaboration – the idea of using the

[16] This is also in contrast to Dr. Kouris' investigation of CD-10 as a surface marker, where he was merely observing and recording inherent properties of the cells as a way to describe them, rather than selecting cells with certain characteristics for a particular purpose. Tr. 5-108:13 to 5-112:16.

new cell to treat multiple sclerosis, the switch to feeder-free and GSK3i, the BM potency screening, the IL-6 screening, the mitotic inactivation – concerned moving the process from the laboratory to the patient, from benchtop to bedside. The Defendants were both trained medical doctors, with expertise in autoimmune diseases and an interest in therapeutic use.

87. Drs. Xu and Wang's improvements to the Kimbrel recipe produced cells that were more numerous, more robust, and better adapted to transition into human trials, from benchtop to bedside. That was a significant contribution in this space. *See* Tr. 6-41:5-10 (scaling up).

88. The regulation of stem cell development was extremely complicated and is still largely unknown. Tr. 7-29:19 to 7-31:2; 7-42:12 to 7-43:3. Wang and Xu's improvements were unexpected, substantial, and meaningful, the product of insight, experience, and hard work.

II. Facts Relevant to the c.93A Claim

A. The '321 Application

89. In 2011, approximately a year into the collaboration, the SCRMI entity ceased operations, Dr. Kimbrel moved over to the ACT entity, and Dr. Lanza assumed control of the collaboration from the ACT side. TX-13 ("We absolutely need to get Bob's approval to continue the collaboration").[17] Lanza announced he was "skeptical of all collaborations" and more aggressively interested in "legal . . . rights." *Id*.

90. On November 30, 2011, Astellas filed U.S. Provisional Patent Application No. 61/565,358 ("'321 Provisional"). TX-35.

91. The '321 Provisional contained many of the Defendants' contributions. Indeed, ACT copied paragraph after paragraph of text from the Defendants' January 2011 UConn grant application into their specification. *Compare* TX-CC-A (Defendants' grant application) *with*

[17] Further evidence of Lanza's tightening grip came in subsequent emails. *See, e.g.*, TX-27 (relaying conversations with "Bob" and Kimbrel's statement that "they won't allow me" to send Wang various data).

TX-35-A (Astellas' '321 provisional patent application); TX-CC-A at 3, 6 *with* TX-35-A at 6,7; TX-CC-A at 6 *with* TX-35-A at 12; TX-CC-A at 7 *with* TX-35-A at 32; TX-CC-A at 8 *with* TX-35-A at 33; TX-CC-A at 9 *with* TX-35-A at 33-35; TX-CC-A at 11 *with* TX-35-A at 35, 36; TX-CC-A at 12 *with* TX-35-A at 42-43.

92. Astellas's '321 Provisional also included various Defendant inventions, including Wang and Xu's concept of using the resulting cells to treat MS; TX-35 at 49-50, Claims 53-54, 57; Wang and Xu's concept of mitotic inactivation; *id*. at 30, ¶¶ 80, 83; and their therapeutic data concerning multiple sclerosis (the only data showing therapeutic effect), *id*. at Fig. 9. Neither Wang nor Xu consented to this use of their ideas. Tr. 10-66:4-6; 10-66:18-21; 10-88:15-18.[18]

93. This '321 Provisional would serve as the basis for the patent applications that later become the '321 patent and the '956 patent.[19] *See* TX-48; TX-FG.

94. ACT did not name Wang and Xu as co-inventors, despite separately claiming many of the foregoing inventions. TX-1; TX-2.

95. ACT did, however, name as an inventors two junior ACT scientists whose employment by ACT would keep the patent entirely owned by ACT: Nicholas Kouris and Jianny Chu. *See* TX-1; TX-2. Dr. Lanza admitted at trial that adding Drs. Kouris and Chu as inventors would have no financial impact on ACT, while adding Drs. Xu and Wang would. Tr. 1-152:17-22.

96. As Dr. Kouris admitted at trial, his role was merely to "characterize" the cell

[18] Dr. Lanza admitted at trial that he had "concerns" about putting information ACT had obtained from Drs. Xu and Wang into the '321 Provisional without seeking permission. Tr. 1-152:20 to 1-156:24

[19] On November 30, 2012, Plaintiff filed both U.S. Non-Provisional Patent Application No. 13/691,349 ("'321 Non-Provisional"), which would later mature into the '321 Patent, and Patent Cooperation Treaty Application No. PCT/US2012/067464 ("'321 PCT Application"). The '321 Provisional formed the basis for both. On June 6, 2013, the World Intellectual Property Organization ("WIPO") published the '321 PCT Application as International Application Publication No. WO2013/082543. In the published copy of the '321 PCT Application, Plaintiff claimed priority to the '321 Provisional Application. *See* TX-48.

created by the existing Kimbrel recipe – *i.e*. to observe and record the cell's emissions of certain proteins. Tr. 2-116:5-12; Tr. 5-117:12-22. As Dr. Kimbrel likewise admitted, ACT added Dr. Kouris to the patent for his work measuring one single secretion, CD10. Tr. 2-116:5-12; *see* TX-1 ('321 patent) (citing various markers, among them CD10).

97. This was the reason he was added to the '956 patent as well. Tr. 2-114:24 to 2-117:1; *see also* Tr. 5-96:21 to 5-99:4.

98. Dr. Kouris did not change the recipe. He did not change the cell. He merely observed it. He measured the amount of one secretion, and wrote down what he found. Astellas deemed that enough to warrant inventorship. *See generally* Tr. 5-99:5 to 5-113:20; Tr. 5-117:12-22; Tr. 2-114:24 to 2-118:6; Tr. 5-99:21 to 101:1 (like counting lights on a Christmas tree).

B. The Confidentiality and Patenting Double-Standards

99. Within days of taking the Defendants' ideas and claiming them as its own, Astellas turned around and demanded a new set of controls. On December 9, 2011, despite having worked with Wang and Xu for more than a year, Kimbrel announced that she had sought approval from Dr. Lanza to continue and that, "[h]e and the board have granted us approval to continue our collaboration with you provided that we can establish and agree to certain details upfront." TX-25 at 1. The email sought to impose new confidentiality requirements for proprietary protocols, cells, and preliminary data. *Id.* at 2.

100. On January 20, 2012, Dr. Lu sent Dr. Xu a draft material transfer agreement ("MTA") attempting to cast the relationship in terms of "materials," and bearing a new set of confidentiality provisions. TX-UB at 5 (MTA at §5).

101. The draft also contained a section devoted to patent rights to cover the possibility of "Recipient's research results in an invention." *Id*. at 4 (MTA at §4). Because UConn had presumptive rights in their employees' inventions, Xu forwarded the MTA draft to UConn's

Director of Technology Licensing, who then proposed edits to Astellas. TX-XU.

102. Less than a month later, Astellas sought to claw back its own proposal. UConn proposed that Astellas would be automatically permitted to use but not commercialize any of the Defendants' inventions. TX-XU at 3 (edits to §4(c)). Matt Vincent, Astellas's Director of Business Development (but described by Dr. Lu as "their lawyer," Tr. 6-132:21-22, *see also* 10-38:11-15) responded by proposing that the parties "take patent filing off the table," *i.e.* removing the patent provisions that Astellas had itself proposed. TX-XV at 3. The Court finds that Astellas was keenly aware of the possibility of Defendants making patentable inventions. *Id.*

103. With UConn's blessing, Drs. Wang and Xu refused to execute the MTA because it did not protect their intellectual property rights. Tr. 6-119:12-16; Tr. 10-41:19 to 10-42:6.

104. In March 2012, Dr. Kimbrel asked Dr. Wang for data from the collaboration for Astellas's internal use. Tr. 2-119:2-18; TX-FI at 1. Dr. Wang agreed. *Id.*

105. In April 2012, Astellas began to renege on the parties' agreement for an academic paper. The parties had originally agreed to draft a single joint paper. Tr. 10-79:16-19; *cf.* TX 13 (Lanza proposed rules of authorship on the joint paper). Kimbrel announced that "Bob" and the Astellas CEO had determined that the parties should in fact submit two papers, not one. TX-27 at 2. Dr. Xu agreed to the proposal, thinking ACT's paper would be entirely separate from his work and contributions. Tr. 10-80:22 to 10-81:4.

106. In early June 2012, a stranger contacted UConn asking about Defendants' confidential information and the status of the collaboration. TX-XX. Dr. Wang investigated and determined that the video and data that he had given to Dr. Kimbrel several weeks before – relying on her promise to use it only "in house," *see* TX-FI. – had in fact been shared at an ACT investor's meeting in London and on the ACT website. Tr. 1-196:18-24; Tr. 2-120:4-6; TX-MV.

107. Wang worried the data release would jeopardize his publication. Tr. 6-134. He feared other companies could scoop the data and publish, or advance their own commercial development. Tr. 6-135. Wang was also worried that the information might get caught up in alleged insider trading at ACT. *Id.* He worried, too, that patients might start approaching UConn before the therapy was ready for use. Tr. 6-135:12-16.

108. On June 8, 2012, Dr. Wang reached out to Astellas via an email to Dr. Kimbrel. TX-MV at 3. Astellas's response was inconsistent. After blaming SEC insider trading, Dr. Lu stated that Dr. Lanza had "just showed a frame of your video." *Id.* at 2. Within hours, Mr. Vincent contradicted that account, stating that the videos had been played and that it was ACT's CEO (not Lanza) who made the unauthorized disclosure. *Id.* at 1.

109. Despite telling the Defendants that they had a "heavy heart," *id.* behind the scenes – and again at trial – Astellas derided the Defendants as melodramatic. Tr. 1-190:19-24.

C. The '551 Patent Application

110. Shortly after learning that Astellas had published his data, Dr. Wang began drafting a provisional patent application. Tr. 6-136:17-23.

111. On July 12, 2012, Xu and Wang filed U.S. Provisional Patent Application No. 61/670,787 ("'551 First Provisional Application"). TX-3.

112. This was a rough "provisional" application – drafted without the help of a lawyer – on certain aspects of their improved version of the original HB-MSC protocol. Tr. 6-139:24 to 6-141:8.

113. Drs. Wang and Xu did not name Kimbrel and Lanza as co-inventors.[20] *Id.* The application was not focused on the Kimbrel and Lanza contribution. It referenced the base

[20] The Court has since determined that Wang and Xu should have named Kimbrel and Lanza as co-inventors. *See* ECF 163.

Kimbrel protocol but other than a single introductory claim announcing the *making* of the HB-MSC, *see* TX-3 at 3 (claim 1), the remaining 26 claims are directed to Drs. Xu and Wang's own idea of *using* the cells to treat multiple sclerosis, related autoimmune diseases, and the therapeutic features of the diseases and their treatment. *Id.* at Claims 2-19 (multiple sclerosis), 20 (multiple sclerosis), 27 (T-cell regulated autoimmune disease)[21]

114. Dr. Wang and Xu's provisional application contained many of the Defendants' inventive contributions. *See, e.g.*, TX-3 at 9 (Abstract) (reciting *inter alia* mitotic inactivation via "irradiation," comparison of BM-MSCs "immunosuppressive" function, and treatment of multiple sclerosis).

115. The Court finds that Drs. Wang and Xu were not acting in a deceptive manner when filing their patent application. Rather, the Court credits their testimony that they were acting defensively and attempting – poorly, as it turned out – to protect (i) their contributions to the HB-MSC process and (ii) the use they had proposed: treating multiple sclerosis. Tr. 6-140:18 to 6-141:8; 6-141:21 to 6-142:6; *see also* Tr. 10-41:14-18 (always thought he had right to patent his ideas); TX-3 at claims 2-19; TX-9 at 10-11.

116. Dr. Wang used intemperate language in some internal emails to describe the patent application but as he explained at trial (and the Court credits), it was drafted and filed in a fundamentally defensive posture at a time when Astellas had violated his trust and he had good cause to worry that Astellas might do him harm. Tr. 6-139:1-20.

D. Formation of ImStem Based on Different Technology

[21] Their second provisional patent application, Xu and Wang filed U.S. Provisional Patent Application No. 61/762,961 ("'551 Second Provisional Application"), filed on February 11, 2013, was much the same: drafted without the aid of a lawyer, containing Defendants' inventions (e.g. IL-6), and with claims directed to therapeutic effect rather than the recipe itself. TX-9 at 10-11.

117. While the parties' collaboration developed, Drs. Xu and Wang undertook a different project.

118. By early 2012, Drs. Xu and Wang had finalized a new, completely different recipe. They took Dr. Xu's 2002 hESC-to-trophoblast protocol and added a new step: differentiating the trophoblasts into so-called "T-MSC's."[22] Tr. 6-125:7-14; Tr. 6-193:9-17.

119. The ImStem method of deriving T-MSCs is a different method from the one used to derive HB-MSCs (*i.e.* using hemangioblasts as an intermediate). The T-MSC method does not use hemangioblasts or HB-MSCs or the Kimbrel protocol. It uses different chemicals in different concentrations. Tr. 6-125: 2 to 6-126:4; Tr. 6-126:11-13; Tr. 10-49:1-17.

120. The new T-MSC protocol was simpler, faster, more consistent, cheaper, and more easily scaled than the HB-MSC protocol. Tr. 6-125: 21 to Tr. 6-126:4; Tr. 10-50:17-25.

121. In June 2012, Drs. Xu and Wang formed a company, ImStem, to pursue their T-MSC technology. ECF 114 ¶ 47; Tr. 6-125:7-10.

122. At trial, Astellas' Dr. Fortier pointed to deposition testimony from Dr. Xu that supposedly called working with Astellas a "shortcut" for ImStem's T-MSC technology. Tr. 3-119:4 to 3-120:2. When pressed, however, Dr. Fortier could not explain what the alleged "shortcut" was or what Dr. Xu meant by his use of the term. Tr. 3-173:1 to 3-174:25.[23]

123. Based on the evidence at trial, the Court finds the existence of the EAE model was a "shortcut" for the new company only insofar as it facilitated the process of testing the new T-MSCs. Tr. 10-59:3-19. The collaboration had caused Dr. Xu to get an animal use permit for UConn. Tr. 10-59:6-14. Once that permit was in place and the EAE mouse model had been

[22] Dr. Xu testified they had been working on the T-MSC recipe as early as 2011. Tr. 10-205:15 to 10-209:17

[23] Astellas' damages expert likewise could not explain what the alleged "shortcut" was. Tr. 5-87:23 to 5-88:7.

built, that tool could be put to other uses. Tr. 10-59:15-19. The Court credits Dr. Xu's testimony that that is what he meant by "shortcut." *Id.*

124. The Court does not credit Dr. Fortier's testimony regarding this topic because *inter alia* she admitted on cross-examination that she did not actually know how Dr. Kimbrel's technology allegedly affected the T-MSC technology. Tr. 3-174:15-20.

125. Several ImStem business plans (including one from July 2012) and investor presentations highlight the advantages of hESC-MSCs to adult tissue-derived MSCs, as well as technological advantages of the ImStem trophoblast differentiation (*i.e.* T-MSC) method. TX-19; TX-AH; TX-AJ.

126. While the earliest draft of the ImStem business plan (disclosed to just one investor, Dr. Men) contained one reference to the HB-MSC cell in a graph of data, that draft was never acted upon and quickly replaced. Tr. 6-125:7-10; TX-19. Dr. Men testified at his deposition that he had never heard of HB-MSCs and made his investment decisions based upon Dr. Xu's reputation and T-MSCs. *See* TX-YO (45:2-12; 48:10-25; 154:17-21). The later versions of the business plan focused on T-MSCs.[24] *See* TX-AH; Tr. 6-125:7-10.

127. Drs. Wang and Xu never disclosed the HB-MSC protocol to their investors, none of whom would have understood it if they had. *See* Tr. 6-188:12-18.

E. Astellas Discovers ImStem

128. In May 2013, Astellas learned that Wang and Xu had formed ImStem. Tr. 6-125:7-10; *see* Tr. 6-145:8 to 6-146:4; TX-IK.

129. On May 21, 2013, Lu informed Lanza that he had learned that Defendants had

[24] At trial, Astellas pointed to a scattering of references to the '551 PCT Application in ImStem investor materials, but Astellas failed to adduce any evidence to suggest that any investor acted upon (or even understood) such information.

formed their own stem cell company. Lu transmitted a link to ImStem's website to Lanza. In this email, Lu stated: "As we discussed last week in DC and today, I just learned (on May 12) that the UConn group we collaborated with our MSC project formed their own stem cell company." *See* TX-OF.

130. On May 30, 2013, Astellas filed U.S. Non-Provisional Patent Application No. 13/905,526 ("'956 Non-Provisional"), which would later mature into the '956 Patent.[25] TX-FG. Claim 1 of the application included the invention of using HB-MSC cells to treat MS, the idea Wang had proposed in his first meeting in Marlborough, MA – and the only treatment/concept for which Astellas had had data at the time of the original application. TX-35 at Fig. 9.

F. Publication of the '321 in June 2013 (Closing the Damages Window)

131. On June 6, 2013, the '321 PCT Application published and disclosed the contents of the four-step Kimbrel protocol, namely the precise steps required to differentiate (1) hESCs into (2) embryoid bodies, then (3) hemangioblasts, then (4) MSCs. The '321 PCT Application contained a corresponding set of draft claims, also setting forth – publicly – the basic Kimbrel protocol. *See* Tr. 8-146:8-13; Tr. 8-147:2-17; *see also* TX-48.

132. As of that date, there were no products practicing the claimed inventions by either party. Astellas had commercialized nothing. There was no revenue from any claimed inventions. Tr. 9-23:14 to 9-24:2. Neither company had HB-MSC customers of any kind. *Id.; see* Tr. 9-26:15 to 9-27:12. Neither company lost any such sales. *Id.* Neither company had lost any commercial opportunities related to HB-MSCs. *Id.* Neither had lost market value.[26]

133. Astellas had not suffered actual harm of any kind – a point both sides experts

[25] The '956 Non-Provisional was filed as a "Continuation-in-Part" of the '321 Non-Provisional, which means that the '321 Non-Provisional (and by extension the '321 Provisional) formed the basis for the '956 Non-Provisional.

[26] Since then, neither the Defendants nor the Plaintiff have ever licensed or commercialized any process or product that employs any of the patents-in-suit. Tr. 9-26:15 to 9-27:12.

agreed upon at trial. Astellas' damages expert, Dr. Bell, did not offer any opinion that Astellas had suffered any actual losses, compensatory damages, incidental damages, or that Astellas has suffered any lost profits. Tr.5-42:18-23; Tr. 5-43:10-17; Tr. 5-49:8-11; Tr. 5-49:14-19; Tr. 5-50:13-18; Tr. 5-51:13-23; Tr. 5-51:24-25; Tr. 5-52:1-4.

134. Twenty-one days later, on June 27, 2013, Wang and Xu filed their own PCT application – Application No. PCT/US2013/048291 ("'551 PCT Application"). Tr. 8-146:2-4; TX-40. The '551 PCT Application was the basis for the '551 national stage and thus has the same specification and figures as the '551 patent. Tr. 8-143:25 to 8-144:1-9; TX-40.[27]

135. The '551 PCT application was substantially revised from the earlier '551 provisional applications. TX-40. Wang had discovered the now-published Kimbrel/Lanza application (the '321 PCT Application) and substantially rewrote the '551 PCT application, this time with the assistance of counsel. Tr.6-150:16 to 6-151:2.

136. The new claims specifically called out many of the Defendants' inventions. Tr. 8-194:8 to 8-197:14.

137. All of Drs. Xu and Wang patent applications – the original '551 provisional applications and the subsequent '551 PCT – remained confidential (*i.e.* known only to the PTO, which had already received the same information seven months earlier) until after the '321 patent application became public. Tr.8-141:20 to 8-142:2; Tr. 8-146:1-4.

G. Astellas Discovers More About ImStem

138. On June 28, 2013, Kimbrel sent her colleagues an email titled, "[K]eep eye on UConn patent pending." TX-NW. She then stated, in the body of her email:

> http//:www.ctmirror.org/story/stem-cell-grants-target-multiple-sclerosis-epilepsy-cancer. [S]ee story for bit on ImStem, the new

[27] Drs. Xu and Wang also patented their T-MSC technology. Tr. 6-154:14-16; TX-GB. ImStem used a stem cell line that it licensed and obtained from a third party (not Astellas) to derive it. TX-GB at 14:64 to 15:3; 56:34-35.

> company that our "collaborators" formed to continue exploring hESC-derived MSCs for Multiple Sclerosis.

The attached article stated that the Defendants had started a company to use cells for the treatment of multiple sclerosis and that there was a patent pending. *See* TX-NW.

139. Mr. Vincent of ACT (described by Dr. Lu as "their lawyer," Tr. 6-132:21-22, *see also* 10-38:11-15) replied that he had already seen the article and had been "checking" – presumably for the patent application referenced in the subject line – for a week. TX-NM.

140. Astellas thus knew that ImStem was pursuing to the development of hESC-derived MSCs to treat multiple sclerosis. TX-NM; TX-NW. Astellas believed ImStem was pursuing the subject matter of the parties' collaboration, and was concerned. TX-NM; TX-NW.

H. Later Events

141. In late 2013, Drs. Xu, Wang, Lanza and Kimbrel submitted a joint article for publication in the prestigious journal, Cell Stem Cell. In March 2014, the editor notified Dr. Xu that the article had been rejected, noting that the "overall novelty" of the article had been "undercut to a fairly significant degree" by a recently published article authored by Lanza and Kimbrel reporting on the same subject as the joint article. TX-DZ at 2. Dr. Xu complained to Dr. Lanza that "somebody among us has killed our [joint] paper." TX-DZ at 1.

142. The article was published in a less prestigious journal, Stem Cell Reports, in July 2014. TX-9.[28]

143. In June 2016, the Defendants voluntarily disclosed a copy of the '321 PCT application (published as WO2013/0825543) to the PTO as part of their own patent prosecution for what became the '551 patent. Tr. 8-150:9-12; Tr. 8-151:1-18; TX-40C.

144. The PTO Examiner – upon comparing the two applications – determined that the

[28] Dr. Lanza waited to pursue any legal claim, wanting to "let [their joint] paper get to press" first. TX-EB.

claims were substantively identical.[29] Tr. 8-152:2-12; TX-40. The '321 PCT application contained not only the basic Kimbrel protocol but also ideas Astellas had previously copied from the Defendants (*e.g.* mitotic inactivation) plus now screening/selecting for greater-than-BM-MSC potency. *See, e.g.*, TX-1 (same specification as PCT) at col. 50, ln. 4-8, 29-45.

145. On July 28, 2016, the PTO rejected the Defendants' claims as anticipated by Astellas' earlier-filed '321 PCT application. Tr. 8-149:20-25; TX-40D at 6-7.

146. In response to the PTO rejection, the Defendants filed a Response under 37 C.F.R. § 1.111 and amended Claim 1 to affirmatively require the step of culturing hESCs in a serum-free medium "with at least one GSK3 inhibitor at a concentration ranging from 0.05 uM to 0.2 uM, wherein the hESCs are cultured in the absence of feeder cells." Tr. 8-149:13-19; Tr. 8-152:13 to 8-153:1; TX-40E at 2.

147. The Defendants argued that the Astellas '321 PCT did not include this limitation and that their amended claim (with GSK3i) was therefore novel and non-obvious. TX-40.

148. The Examiner agreed. Tr. 8-150:24 to 8-151:7; 8-155:1-6. In the Reasons for Allowance, the Examiner stated that the claims were allowable because "the claims now require the presence of a GSK3 inhibitor at a specific concentration that results in the production of hESC-MSCs with the specific characteristics recited by the claims." TX-40F. The Examiner continued, "[t]his limitation overcomes the rejections of record [i.e., in the 28 July 2016 Non-final Office Action]." *Id.* In short, according to the Examiner, the addition of GSK3i was sufficient to overcome the Examiner's prior novelty and obviousness rejections. Tr. 8-154:2-24; TX-40. The addition of GSK3i – one of Wang and Xu's contributions – was novel and non-

[29] At that point, the Defendants' claim 1 had recited the *optional* step of culturing hESCs with a GSK3 inhibitor.

obvious.[30] *Id.*

149. More than four years after "keeping an eye" on their new competitor, three-and-a-half years after reviewing the '551 PCT Application and concluding it might cause "litigation," and more than three years after internally articulating their legal rights, Astellas finally filed suit. (ECF 001).

150. At trial, Astellas's damages expert (Dr. Bell) did not quantify any time or money Astellas allegedly lost, nor did he attempt to determine any lost compensation or royalties. Tr. 5-42:13-23. He likewise did not quantify: (i) any impact on Astellas' purchase of Ocata (ACT had changed its name by this point) or what portion of that transaction could attributed to the '321 or '956 patents; Tr. 5-42:24 to 5-44:25; (ii) Astellas' own value as a basis for damages; Tr. 5-52:11 to 5-53:11; or (iii) the value any of the patents-in-suit or the technologies at issue; Tr. 5-50:24 to 5-52:4l; Tr. 6-26:4-14.

151. Both he and Defendants' damages expert (Mr. Green) agreed that during the relevant time period Plaintiff did not lose: any customers, any profits, any revenue, any opportunities, any market value, or any investments, nor did Astellas or ImStem even have FDA approval to conduct clinical trials or have a commercial product on the market. Tr. 5-48:10 to 5-50:19; *see* Tr. 9-23:14 to 9-24:5.

152. The "implied value" of ImStem as described by Dr. Bell is not an accurate proxy for the value of any allegedly-taken Astellas technology (and is in any event legally inapplicable, *see infra*). Tr. 9-25:17 to 9-26:14, -14Tr. 9-28:20 to 9:29:7; *see also* Tr. 9-21-7 to 9-22:10, 9-43:1-13, 9-25:17 to 9-26:3.

[30] Drs. Wang and Xu also filed a declaration under 37 C.F.R. § 1.131 "swearing behind" the Lanza and Kimbrel application but the declaration was mooted by the Examiner's determination that the use of GSK3i was novel and non-obvious. It is not evident from the record that the Examiner reviewed the declaration. Tr. 8-155:23 to 8-156:5.

CONCLUSIONS OF LAW

I. Inventorship

153. For the reasons set forth below, the Court finds that all four scientists in the collaboration should have been named as inventors on all three patents-in-suit., and all should be so named today (with the exception of Dr. Xu on the '956 patent).[31]

A. Law

154. The parties' claims for correction of inventorship arise under 35 U.S.C. § 265.

155. Joint inventorship "is one of the muddiest concepts in the muddy metaphysics of the patent law." *Dana-Farber Cancer Inst., Inc. v. Ono Pharm Co..*, 379 F.Supp.3d 53, 82 (D.Mass. 2019) *affd*, 964 F.3d 1365 (Fed. Cir. 2020) "Inventorship is a mixed question of law and fact: The overall inventorship determination is a question of law, but it is premised on underlying questions of fact." *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1362 (Fed. Cir. 2004).

156. "[T]he critical question for joint conception is who conceived, as that term is used in the patent law, the subject matter of the claims at issue." *Falana v. Kent State University*, 669 F.3d 1349, 1357 (Fed. Cir. 2012) (*citing Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998).

157. "A contribution to one claim is enough" to qualify a joint inventor. *Id.* A co-inventor does not need to make a contribution to every claim of a patent. *Ethicon*, 135 F.3d at 1460. Nor does a co-inventor need to contribute to the conception of all the limitations in a single claim. *Eli Lilly*, 376 F.3d. at 1361. *See also Eli Lilly*, 376 F.3d at 1358 ("no explicit lower

[31] Dr. Xu should have been named on the '956 patent as well but he delayed bringing the claim and I therefore deemed him ineligible. *See* ECF 85 at 10-11. The Court now recognizes that Dr. Xu's relative isolation in Macau and the 13-hour time difference between Boston and Macau surely inhibited his participation in this case. The Court will entertain a motion for reconsideration on that point.

limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor").

158. "All inventors, even those who contribute to only one claim or one aspect of one claim of a patent, must be listed on that patent." *Vapor Point LLC v. Moorhead*, 832 F.3d 1343, 1348–49 (Fed. Cir. 2016); *Fina Oil and Chemical Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) ("One need not alone conceive of the entire invention, for this would obviate the concept of joint inventorship.").

159. Since "[p]atent issuance creates a presumption that the named inventors are the true and only inventors," to establish co-inventorship, the alleged co-inventor "must prove [his or her] contribution to the conception of the claims by clear and convincing evidence." *Ethicon*, 135 F.3d at 1460–61 (Fed. Cir. 1998).

160. When an invention is made jointly, "the joint inventors need not 'physically work together or at the same time,' 'make the same type or amount of contribution,' or 'make a contribution to the subject matter of every claim of the patent.'" *Vapor Point*, 832 F.3d at 1349 (quoting 35 U.S.C. § 116).

161. The Federal Circuit has explained that "[a]ll that is required of a joint inventor is that he or she (1) contribute in some significant manner to the conception or reduction to practice of the invention, (2) make a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art." *Israel Bio-Eng'g Project v. Amgen, Inc.*, 475 F.3d 1256, 1264 (Fed. Cir. 2007).

162. "Conception is defined as the formation in the mind of the inventor, of a definite

and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Stern v. Trustees of Columbia Univ.*, 434 F.3d 1375, 1378 (Fed. Cir. 2006).

163. "Conception is complete when 'the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation.'" *Stern*, 434 F.3d at 1378 (quoting *Burroughs Wellcome*, 40 F.3d at 1228). "In a joint invention, each inventor must contribute to the joint arrival at a definite and permanent idea of the invention as it will be used in practice." *Univ. of Pittsburgh of Commonwealth Sys. of Higher Educ. v. Hedrick*, 573 F.3d 1290, 1298 (Fed. Cir. 2009).

B. The '551 Patent

164. For Count I, Plaintiff has not met its burden that Drs. Wang and Xu should be removed from the '551 patent.

165. Drs. Xu and Wang made (at least) the following contributions to the inventions claimed in the '551 patent:

- The use of a specific range of GSK3i in a serum-free, feeder-free medium in the first stage of the recipe, as that concept appears in Claim 1(a) ("culturing human embryonic stem cells in a serum free medium comprising at least one GSK3 inhibitor at a concentration ranging from 0.05 μM to 0.2 μM, wherein the human embryonic stem cells are cultured in the absence of feeder cells");
- The use of a specific GSK3i, "BIO," as that concept appears in Claim 11;
- Screening/selecting HB-MSCs with low IL-6 expression, as that concept appears in Claim 1(e) ("comprise less than 2% of cells expressing IL-6");
- Mitotically inactivating the HB-MSCs, as that concept appears in Claim 6 ("further comprising a step of irradiating the human mesenchymal stem cells) and Claim 7 ("wherein the human mesenchymal stem cells are irradiated with gamma-irradiation").

166. The concept of using of a specific range of GSK3i in a serum-free, feeder-free medium in the first stage of the recipe was substantial and non-obvious.

167. As noted above, this particular dose of GSK3i: (i) had never been deployed in this

kind of four-step recipe; (ii) was never part of Kimbrel's original feeder-based protocol; (iii) was necessitated by Dr. Wang's deliberate decision to refashion the recipe as a feeder-free process to facilitate eventual FDA approval; (iv) ran counter to the conventional wisdom that GSK3i would prevent (rather than promote) differentiation; and (v) created unexpectedly positive results in the later stages.

168. Dr. Wang and Xu's use of GSK3i improved both quality and quantity, which are critical for real-world deployment.

169. These contributions alone are sufficient to warrant Wang and Xu's continued presence on the '551 patent.

170. Further, the Examiner's finding that the addition of GSK3i was non-obvious during the prosecution of the '551 patent (in the "Reasons for Allowance") is further compelling evidence that this particular use, in this particular range, in this particular context, was non-obvious and not insubstantial. *See* Tr.8-140:21 to 8-141:5; 8-144:25 to 8-145:1-15; 8-149:20-25.

171. Generally, if a Patent Examiner raises a prior art rejection on the basis of novelty (35 U.S.C § 102) or obviousness (35 U.S.C § 102), an applicant is entitled to present arguments rebutting the Examiner's conclusions and/or submit amendments to the claims in order to obviate the rejection. *See* MPEP §§ 706-707, 2141 (II); *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). For example, an applicant can amend the claims to include an element not described or suggested by the cited art. *See* MPEP § 714.

172. Once presented with such an amendment, the Examiner will again consider the proposed claims in view of the statutory requirements. If the Examiner concludes that the amendment adds enough so that the amended claims are both novel and non-obvious over the prior art, the Examiner will then allow the claims with an explanation of the Reasons for

Allowance. *See* 37 C.F.R. § 1.104 (e); MPEP § 1300.

173. The foregoing process happened here. Tr. 8-149:20-25. As noted above, the Examiner stated in his Reasons for Allowance that the addition of 0.05uM to 0.2 uM GSK3 GSK3i in a feeder-free, serum-free first stage was sufficient to overcome his prior novelty and obviousness rejections. TX-40 at AIRM00295969-970. The PTO thus deemed the addition of GSK3i to be novel, non-obvious, and sufficiently substantial to warrant a patent.

174. Lanza and Kimbrel contributed nothing to this inventive feature.

175. The Court likewise credits Dr. Perry's testimony that Dr. Wang's decision to use a particular GSK3i, BIO – which had by 2010 been eclipsed by other, more common inhibitors – is also significant and contributed to the success of the protocol. Tr. 8-49:13 to 8-50:4. The Court finds this to be another ground for keeping Drs. Wang and Xu on the '551 patent.

176. The concept of screening/selecting HB-MSCs with low IL-6 expression was also substantial and non-obvious.

177. The contribution was non-obvious because *inter alia*, as noted above: (i) not all batches of HB-MSCs turn out the same; (ii) IL-6 levels in a given batch change over time with increased re-plating "passages;" (iii) the Defendants were the first to substantively explore the role of IL-6 and recognize its significance (while the other scientists in the collaboration shelved the raw data and never explored its therapeutic significance); (iv) prior scientists believed high levels were desirable; (v) the Defendants developed a hypothesis and tested it, understanding the role of IL-6 (not just observing the amount) ; (vi) their analysis and idea of preferentially seeking low-IL-6 cells ran counter to the conventional wisdom in the art. *See supra* ¶¶ 72-78.

178. The Court further credits Dr. Bunnell's testimony that the concept of specifically using/choosing low-IL-6 cells for MS treatment was novel and surprising. Tr. 7-83:23 to 7-84:7.

179. The Court also finds that the contribution is substantial in the context of the patent. All of the inventors acknowledged the significance of IL-6 in their joint 2014 paper. TX-9 at 115 (Summary), 121. Further, to the extent choosing low IL-6 cells improves therapeutic efficacy, that is a significant goal of the '551 patent.

180. The concept of mitotically inactivating the HB-MSCs was substantial and non-obvious.

181. The contribution was non-obvious because *inter alia*, as noted above, (i) the notion had only been explored *in vitro*, and only in other kinds of cells for other diseases; (ii) behavior *in vitro* was not predictive of behavior *in vivo*; (ii) the notion had never been explored in connection with live multiple sclerosis models (another Defendant idea); (iv) scientists did not understand how MSC's imparted therapeutic effect; (v) the mechanics of the *in vivo* emissions process were unknown; (vi) no one knew how mitotic inactivation would affect cell mobility, longevity, function, efficacy, toxicity, cell-to-cell communication, for these cells, for this disease, *in vivo*. *See supra* ¶¶ 54-58; Tr. 6-37:12 to Tr. 6-38:7; Tr. 6-72:8-20; Tr. 6-73:1-6; Tr. 6-74:21-24.[32]

182. The Court finds it was also substantial, part of the process of making the protocol and cells suitable for clinical deployment. Tr. 6-74:21 to 6-75:2.

183. These contributions further warrant Wang and Xu's continued presence on the '551 patent.

C. The '956 Patent

184. For Counterclaim Count I, Defendants have met their burden they should be

[32] As noted above, Plaintiff's own expert (Dr. Brivanlou) admitted that this was an inventive contribution. Tr. 4-104:13 to 4-106:18.

added to the '956 patent.

185. Drs. Xu and Wang made (at least) the following contributions to the inventions claimed in the '956 patent:

- Treating multiple sclerosis by means of administering a therapeutically effective amount of HB-MSCs, as that concept appears in Claim 3 ("The method of claim 1, wherein the disease or disorder is selected from multiple sclerosis") and Claim 4 ("The method of claim 1, wherein the disease or disorder is uveitis, an autoimmune disorder, an immune reaction against allogeneic cells, [or] multiple sclerosis");

- Mitotically inactivating the HB-MSCs, as that concept appears in Claim 5 ("wherein the mesenchymal stromal cells (a) are mitotically inactivated");

- Screening/selecting HB-MSCs with low IL-6 expression, as that concept appears in Claim 1(e) ("(f) in a resting state, express mRNA encoding interleukin-6 at a level which is less than ten percent of the IL-6 mRNA level expressed by mesenchymal stromal (IL-6) cells, in a resting state, derived from bone marrow or adipose tissue; and/or");

- Screening/selecting HB-MSCs with a therapeutic potency greater than BM-MSCs, as that concept appears in Claim 10 ("wherein the mesenchymal stromal cells have a potency in an immune regulatory assay greater than the potency of bone marrow derived mesenchymal stromal cells").

186. The concept of treating multiple sclerosis by means of administering a therapeutically effective amount of HB-MSCs is substantial and non-obvious.

187. The contribution is substantial because *inter alia* multiple sclerosis is a serious and incurable autoimmune disease afflicting young adults. TX-A at col. 1, ln. 55 – col.2, ln. 10.

188. The significance of this contribution is highlighted by the claims. The claims of the '956 are primarily directed to *using* HB-MSCs to treat certain diseases, not to the *making* of the cells themselves. TX-2 at claims 1-11.

189. Astellas therefore cannot claim exclusive inventorship of the '956 patent based on its contribution of the original Kimbrel protocol for making HB-MSCs or the original HB-MSC

cells themselves.[33]

190. The inventions claimed in the '956 patent concern individual/specific treatments. Claims 3 and 4 identify treatments, including multiple sclerosis. Claim 1 (treating any disease in the world), by comparison, is so broad as to be poorly supported, 35 U.S.C. § 112 (pre-AIA) (enablement), and untethered to Lanza and Kimbrel's actual contributions.

191. The significance of multiple sclerosis is also apparent from the prosecution history. It was the only treatment/concept for which ACT had data in the original '321 provisional application to which the '956 claims priority.

192. As a threshold matter, the Court finds that it was Drs. Wang and Xu (with Dr. Lu) who conceived of the idea. Dr. Lanza's contribution of one question in one email, TX-38 ("any chance we might . . . ?"), was little more than a query or starting point, not "a definite and permanent idea of the complete and operative invention" with respect to multiple sclerosis. *Stern*, 434 F.3d at 1378; *Hedrick*, 573 F.3d at 1298.

193. The idea of using HB-MSC's was not – as of this September 2009 email which never mentions multiple sclerosis – "so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Stern*, 434 F.3d at 1378. Multiple sclerosis was not yet highlighted, let alone tested.

194. Drs. Xu and Wang's contribution is corroborated by the various emails surrounding their summer 2010 meetings, which memorialize the birth of the collaboration and

[33] This distinction between making and using, whether for new or existing compounds, is recognized in the law. 35 U.S.C. § 101 (distinguishing between "process" and "composition of matter" claims). By way of example, the original method patent for the erectile dysfunction drug, Viagra, claimed a novel use for a pre-existing compound. *See* U.S. Patent No. 6,469,012. The compound had been known for years in treating heart disease and high blood pressure. *Id.* at 1:46-61. But as the inventors explained, "Unexpectedly, it has now been found that these disclosed compounds are useful in the treatment of erectile dysfunction," a different disorder and a patentably new use.

their first idea: using HB-MSCs to treat MS. *See, e.g.*, TX-11, TX-16.

195. Drs. Xu and Wang's contribution was not obvious. As noted above: (i) Drs. Xu and Wang were the first to fully conceive of the idea of using the new cells to treat multiple sclerosis; (ii) Drs. Kimbrel and Lanza were not even present at the initial meetings; and (iii) it was not until Dr. Lu reported back to Dr. Kimbrel about the Xu proposal that the MSC program restarted.

196. Further, the prior art to which Astellas's expert (Dr. Fortier) pointed at trial concerned only BM-MSCs and other adult-tissue-derived cells; embryonic-cell-derived MSCs had never been tried *in vivo*. *See* TX-HU; TX-58. Further, the prior art to which she pointed related to safety, not therapeutic effect. *See id.*; *see also* Tr. 6-98:15-25.

197. Further, the Court does not credit Dr. Fortier or Drs. Kimbrel and Lanza regarding this contribution, in part, because Astellas is barred by assignor estoppel.

198. "Assignor estoppel prevents a party who assigns a patent to another from later challenging the validity of the assigned patent." *Mentor Graphics Corp. v. Quickturn Design Sys., Inc.*, 150 F.3d 1374, 1377 (Fed. Cir. 1998) (citing *Diamond Scientific v. Ambico, Inc.*, 848 F.2d 1220, 1224 (Fed. Cir. 1988)); *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 836–37 (Fed. Cir. 1991) (patent assignor may not later contend that invention was valueless). The doctrine bars a similar challenge by any party in privity, *id.*. which Astellas is in this context.

199. Here, Dr. Fortier disparaged the application of HB-MSCs to multiple sclerosis as obvious. Tr. 3-27:10-18. Astellas' disparagement of the multiple sclerosis contribution – the idea of targeting MS – amounts to an assertion that claims 3 and 4 are obvious and thus invalid. *Id.* Claims 3 and 4 constitute a substantial portion of the '956 patent.

200. Having told the PTO that claims 3 and 4 are patentable by dint of the treatment of

multiple sclerosis, Astellas cannot now be heard to argue the contribution was obvious and the patent substantially less valuable.

201. For the reasons set forth above, the concept of mitotically inactivating the HB-MSCs is substantial and non-obvious.

202. For the reasons set forth above, the concept of screening/selecting HB-MSCs with low IL-6 expression was substantial and non-obvious.

203. Further, in the context of the '956 patent, the claims are directed to screening, not merely observing. Claim 1 would be infringed by any HB-MSC's meeting the elements of Claim 1, regardless of that cell's IL-6 emissions. By contrast, only cells screened for low IL-6 expression would meet Claim 9 (element f). Only those cells, those batches, that meet the low screen infringe.

204. Further, as the Court considers the quantum of contribution sufficient to warrant inventorship, the Court finds Dr. Kouris' role instructive. As noted above, Dr. Kouris' role was merely to "characterize" the cell created by the existing Kimbrel recipe – *i.e*. to observe and record the cell's emissions of certain proteins. Dr. Kouris did not change the recipe. He did not change the cell. He merely observed it. *See supra* ¶ 96-98.

205. Astellas deemed that enough to warrant inventorship, adding Dr. Kouris to the patent for his work measuring one secretion. *Id.*

206. Astellas argued at trial that the contribution of preferentially selecting low IL-6 cells (which Astellas mischaracterized as merely measuring the fixed phenomenon inherent to all HB-MSCs) was not an inventive contribution. *See generally* Tr. 3-71:1 to 3-73:18.

207. Astellas' position regarding IL-6 and BM-MSC's at trial – even assuming the claims were directed to measuring fixed inherent qualities (they are not) – was inconsistent with

its representation to the PTO regarding the sufficiency of Dr. Kouris' measure-only contribution.

208. The doctrine of judicial estoppel is designed to prevent such situations. *RFF Family P'ship v. Ross*, 814 F.3d 520, 527–28 (1st Cir. 2016) (test). The Court applies this doctrine now. *Davis v. D.C.*, 925 F.3d 1240, 1256 (D.C. Cir. 2019) (a court may invoke judicial estoppel "at its discretion"). Astellas must be held to its earlier representation to the PTO regarding Kouris. It cannot in this forum claim that measurement of an identifying marker in a novel cell type is insufficient to meet the standard for inventorship.[34]

209. Further, Drs. Xu and Wang's analysis/ideas/contributions with respect to IL-6 (whose properties are not fixed or uniform) were greater than Dr. Kouris's observation of CD10 (a "marker," *see* Tr. 2-114:15-22).

210. Finally, the concept of screening/selecting HB-MSCs with a therapeutic potency greater than BM-MSCs was not insubstantial and non-obvious.

211. As noted above, (i) the notion of undertaking a potency assay arose from Drs. Wang and Xu's notion of using the cells to regulate the immune system; (ii) it allows practitioners to identify cells for therapeutic use (a separate limitation); and (iii) potency may be donor dependent, age dependent, sex dependent, possibly race dependent, toxin smoking exposure, and media dependent. *See supra* ¶ 66.

212. This was a complex and poorly understood scientific field.

213. The Court finds that Wang and Xu's multiple contributions to the claims of the '956 patent were individually and collectively meaningful, non-obvious, not insubstantial and sufficient to warrant their inclusion a named inventor.

[34] The Court notes that the estoppel is not being used as an affirmative defense, since it does not absolve liability; rather it merely holds Astellas to its prior position. *Cf.* ECF 163 (SJ Order) ("Defendants made representations to the PTO under oath and must be bound by them.")

D. The '321 Patent

214. For Counterclaim Count II, Defendants have met their burden that they should be added to the '321 patent.

215. Drs. Xu and Wang made (at least) the following contributions to the inventions claimed in the '321 patent:

- Mitotically inactivating the HB-MSCs, as that concept appears in Claim 17 ("The mesenchymal stromal cells of claim 14, wherein the mesenchymal stromal cells are mitotically inactivated" and Claim 18 ("The mesenchymal stromal cells of claim 17, comprising at least 106 mesenchymal stromal cells and a pharmaceutically acceptable carrier");

- Screening/selecting HB-MSCs with a therapeutic potency greater than BM-MSCs, as that concept appears in Claim 21 ("wherein the mesenchymal stromal cells have a potency in an immune regulatory assay that is greater than the potency of bone marrow derived mesenchymal stromal cells").

216. For the reasons set forth above, the concept of mitotically inactivating the HB-MSCs –claimed here in the '321 patent – was substantial and non-obvious.

217. Further, in the context of the '321 patent, the contribution was significant because the claims indicate the cells may be used therapeutically. *See* TX-1 at Abstract (cells useful for treating "pathologies"), Claim 21 (cells to be measured by test/assay for immunological response). Mitotic inactivation was part of the process of making the protocol and cells suitable for clinical deployment. Tr. 6-74:21 to 6-75:2.

218. Further, in the context of the '321 patent, the fact that (i) Astellas felt the idea was worth copying from Defendants' UConn grant application and (ii) discussed the process (verbatim) in the specification provide further evidence that Astellas believed the concept to be substantial.

219. Defendants contributed everything of inventive substance to Claims 17 and 18, which are directed to mitotic inactivation.

220. Astellas structured the claims as separate dependent claims, such that some cells could infringe the independent claim but not the dependent claims. Put differently, Astellas separately claimed as an invention the use of those cells that met an additional threshold.

221. Claim 18 reinforces the significance of the contribution. The claim is directed to therapeutic use, pharmaceutical treatment – Drs. Xu and Wang's area of comparative expertise.

222. This was a complex and poorly understood scientific field. Papers and prior art pointed in multiple directions. The science underlying these processes was not well understood.

223. For the reasons set forth above, the concept screening/selecting HB-MSCs with a therapeutic potency greater than BM-MSCs.

224. In the context of the '321 patent, directed to preparing cells for therapeutic treatment, the concept of identifying which cells are suitable for therapy by dint of their increased immunological response (in a dependent claim whose limitation must be separately met) is a substantial contribution to the patent.

225. The Court finds that Wang and Xu's multiple contributions to the claims of the '321 patent were individually and collectively meaningful, non-obvious, not insubstantial and sufficient to warrant their inclusion a named inventor.

II. Unfair Trade Practices Under c. 93A

226. For the reasons set forth below, Plaintiff has failed to carry its burden with respect to its unfair trade practices claim under M.G.L.c. 93A (Count V).

A. Law

227. Plaintiff's sole state-law claim arises under M.G.L.c. 93A, § 11 which governs "trade or commerce" using an unfair method of competition or an unfair or deceptive act. This Court enjoys ancillary subject-matter jurisdiction under 28 U.S.C. § 1367.

B. The Claim is Barred by the Statute of Limitations and Unclean Hands

228. As a preliminary matter, Plaintiff's 93A claim is time-barred. Claims arising under Chapter 93A are subject to a four-year statute of limitations. M.G.L.c. 260, § 5A. ECF 163 at 12-13. The relevant event "starting the clock" is the moment a Plaintiff suffers a loss connected to an unfair or deceptive act. *See International Fid. Ins. Co. v. Wilson*, 387 Mass. 841, 850, 443 N.E.2d 1308 (1983).

229. Under the Massachusetts discovery rule, a plaintiff need not know every offending fact constituting his or her claim. *Riley v. Presnell*, 409 Mass. 239, 243, 565 N.E.2d 780, 784 (1991). Nor does the plaintiff need to be aware of his or her actual injury. *Malapanis v. Shirazi*, 21 Mass. App. Ct. 378, 383–84, 487 N.E.2d 533, 537–38 (1986); *Fidler v. Eastman Kodak Co.*, 714 F.2d 192, 199 (1st Cir. 1983) (prospective plaintiff does not need to be aware of his legal injury at this time). Rather, "[i]t is sufficient that the plaintiff has enough information *to suggest* that he has suffered an injury caused by the defendant's conduct." *Wolinetz v. Berkshire Life Ins. Co.*, 361 F.3d 44, (1st Cir. 2004) (emphasis added); *see also Szymanski v. Bos. Mut. Life Ins. Co.*, 56 Mass. App. Ct. 367, 370, 778 N.E.2d 16, 20 (2002).

230. The relevant inquiry is whether "sufficient facts were available to provoke a reasonable person in the Plaintiff's circumstances to inquire or investigate further." *McIntyre v. United States*, 367 F.3d 38, 52 (1st Cir. 2004). The awareness of such facts must rise to something more than a mere hunch, but even something as minimal as this will establish a "duty to inquire into the possible existence of a claim in the exercise of due diligence" *Id.* (internal citations omitted). Once this duty to inquire is established, the plaintiff will be charged "with the knowledge of what he or she would have uncovered through a reasonably diligent investigation." *Id.*

231. As noted above: (i) on May 21, 2013, Lu informed Lanza that he had learned (on

May 12) that Defendants had formed their own stem cell company; (ii) the article he forwarded specifically referenced ImStem's patent filing; (iii) on June 28, 2013, Kimbrel emailed Vincent telling him to "keep an eye" on the "UConn patent pending," in which Kimbrel mentioned ImStem by name and noted that she was aware of ImStem's purpose to "continue exploring hESC-derived MSCs for Multiple Sclerosis;" (iv) multiple sclerosis was the subject of the parties' collaboration; (v) Vincent replied that he had already seen the article and had been "checking" – presumably for the patent application referenced in the subject line – for a week.

232. Based on this evidence, Astellas knew or should have known that Drs. Wang and Xu were using the technology that Astellas now claims as its own. Astellas had a duty to inquire. It failed to do so at every turn. "The law ministers to the vigilant not to those who sleep upon perceptible rights." *Puleio v. Vose*, 830 F.2d 1197, 1203 (1st Cir. 1987).

233. Plaintiff's claim under Mass. G.L. 93A is past the four-year statute of limitation proscribed by M.G. L. c. 260, § 5A, and is therefore time barred.

234. Plaintiff's 93A claim is likewise barred by the doctrine of unclean hands. While 93A sounds in law and makes available a legal remedy (sought here), the underlying statute is *sui generis*, *Kattar v. Demoulas*, 433 Mass. 1, 739 N.E.2d 246, 257 (2000) and premised at least in part on the fact question of a defendants' "unfair" actions. M.G.L.c. 93A § 11 ("unfair or deceptive").

235. For that reason, perhaps, this Court has found that a 93A claim may be precluded by a plaintiff's own unclean hands. *Spruce Envtl. Techs., Inc. v. Festa Radon Techs., Co.*, 248 F. Supp. 3d 316, 322 (D. Mass. 2017). The Court finds that such a defense is appropriate here.

236. As noted above, Astellas: (i) copied-and-pasted paragraph after paragraph of the Defendants' January 2011 UConn grant into their '321 provisional patent application; (ii)

claimed several of the Defendants' inventions as their own in the '321 and '956 patents, including the concepts of treating multiple sclerosis by means of administering a therapeutically effective amount of HB-MSCs, mitotically inactivating the HB-MSCs, screening/selecting HB-MSCs with low IL-6 expression, and screening/selecting HB-MSCs with a therapeutic potency greater than BM-MSCs; (iii) used the Defendants' data without permission; and (iv) publicized the Defendants' data and videos, without permission, to attract investors.

237. The Court finds that whereas the Defendants were operating in good faith and without the benefit of counsel for most of the relevant period, ACT/Astellas was comparatively sophisticated and its own bad acts more culpable. For that reason, the 93A claim is barred.

C. Plaintiff Has Not Articulated a Viable c.93A Claim

238. Quite apart from the time bar and unclean hands, the Court finds that the Defendants did not violate Chapter 93A.

239. Plaintiff assert two categories of allegedly actionable behavior: (1) the Defendants' failure to name Kimbrel and Lanza on the '551 patent despite it containing elements of Kimbrel's original HB-MSC protocol; and (2) the Defendants' alleged use of confidential Astellas information to build and/or promote their new company prior to June 2013, the close of the damages window.

240. With respect to the first category, filing a patent application was not itself an act of "trade or commerce." M.G.L.c. 93A § 11. "Although Chapter 93A provides broad remedies, it is directed only at unfair or deceptive acts that arise 'in the conduct of any trade or commerce'." *Quincy Mut. Fire Ins. Co. v. Atl. Specialty Ins. Co.*, No. 18-CV-11868-ADB, 2019 WL 3409980, at *4 (D. Mass. July 29, 2019) (quoting c. 93A).

241. "[T]he acts or practices complained of must be 'perpetrated in a business context." *First Enterprises, Ltd. v. Cooper*, 425 Mass. 344, 347 (1997). "Plaintiffs must show

that the defendant had a commercial relationship with the plaintiffs or that the defendant's actions interfered with 'trade or commerce.'" *Id.*

242. Trade or commerce includes "the advertising, the offering for sale, rent or lease, the sale, rent, lease or distribution of any services and any property, tangible or intangible, real, personal or mixed" and also includes "any trade or commerce directly or indirectly affecting the people of this commonwealth." M.G.L.c. 93A, § 1(b).

243. Here, nothing concerning the '551 patent was offered for sale, rent, or lease. Plaintiff presented no evidence that Defendants sold or commercialized the '551 patent application during the damages window.

244. Defendants were securing patent rights. Securing legal rights and making legal assertions, by itself, does not constitute commerce or trade. *Cf. First Enterprises*, 425 Mass. at 347 (taking a legal position in litigation does not constitute trade or commerce under 93A).[35] The fact that a legal right is secured erroneously does not make the legal undertaking a commercial one.

245. Further, as noted above, the Court finds that Drs. Wang and Xu were not acting in a deceptive manner when filing their patent application. Rather, the Court credits their testimony that they were acting defensively and attempting to protect (i) their contributions to the HB-MSC process and (ii) the use they had proposed: treating multiple sclerosis. Tr. 6-140:18 to 6-141:8; 6-141:21 to 6-142:6; *see also* Tr. 10-41:14-18 (always thought he had right to patent his ideas); TX-3 at claims 2-19; TX-9 at 10-11.

246. Defendants did not employ "deception" as contemplated by c. 93A; their silence reflected their beliefs and the normal practice of maintaining confidentiality.

[35] Massachusetts courts have departed from these principles only in the insurance context – not applicable here.

247. With respect to the second category of allegedly actionable behavior (using Astellas information as a "shortcut" for their new business), as outlined above there was no improper "shortcut" or other advantage taken by the Defendants.

248. The Court credits the Defendants' uncontested testimony that ImStem is founded upon T-MSC technology and they raised funds based on it and Dr. Xu's reputation. The Defendants' T-MSC technology is entirely distinct from the plaintiff's HB-MSC recipe.

249. Further, because the Court credits the Defendants' testimony (including Dr. Men's (TX-YO (45:2-12; 48:10-25; 154:17-21)) concerning the basis for investments, see supra¶, there was no trade or commerce associated with or arising from the use of Astellas' allegedly confidential information.

250. HB-MSC technology thus played no meaningful role in the new company's launch.

D. Astellas's Damages Theory is Fatally Flawed

251. Plaintiff's 93A claim fails for another reason: Plaintiff has not (and cannot) meet its burden to prove that it suffered any "actual damage" as a result of Defendants' allegedly improper actions. *Coady v. Wellfleet Marine Corp.*, 62 Mass.App.Ct. 237, 245 (2004) (quoting *Agoos Leather Cos. v. American & Foreign Ins*. Co., 342 Mass. 603, 608 (1961)).

252. Recovery under Chapter 93A "shall be in the amount of *actual damages*." M.G. L. c. 93A § 11 (emphasis added). Under the statute, "actual damage" must be a distinct injury to money or property. *Auto Flat Car Crushers, Inc. v. Hanover Ins. Co.*, 469 Mass. 813, 823–24 (2014) (citing *Baldassari v. Public Fin. Trust*, 369 Mass. 33, 45 (1975) ("'money' means money, not time, and ... 'property' means the kind of property that is purchased or leased . . .").

253. Astellas has not suffered any "actual loss," monetary or otherwise, as a result of Defendants' allegedly improper actions.

254. As noted above, at trial Astellas' damages expert (Dr. Bell) did not quantify any time, money, or compensation allegedly lost; nor any impact on Astellas' purchase of Ocata; nor Astellas' own value as a basis for damages; nor the value any of the patents-in-suit or the technologies at issue. *See supra* ¶¶ 141.

255. As noted above, Plaintiff did not lose any customers, any profits, any revenue, any opportunities, any market value, or any investments. *See supra* ¶¶ 142.

256. Faced with a lack of actual damages, Astellas instead argued that it was entitled to the "implied value" of ImStem as of June 2013. Dr. Bell examined at an equity transaction in ImStem on June 22, 2013 and argued that the number of issued shares (1,603,000) suggested a total "implied value" of $1.6M for ImStem. Tr. 5-65:5-10.

257. While styled as "actual damages," Dr. Bell's claim is, in reality, an unjust enrichment damages claim (which is legally barred) by another name. *Mack.*, 2020 WL 4673522 at *9, *citing Shaulis*, 865 F.3d at 16 (unjust enrichment claim barred by 93A claim).

258. Put differently, Astellas has impermissibly alleged a mere "per se" injury rather than any actual harm to itself. *Shaulis*, 865 F.3d at 10 ("a claim resting only on a deceptive practice, regulatory noncompliance, or the impairment of an abstract right without economic loss" will not suffice.). A "legally cognizable injuries under Chapter 93A must involve objective, 'identifiable' harm that goes beyond the deception itself." *Id.*

259. Further, Chapter 93A damages may not include disgorgement-type remedies where – as here – there are alternative way of calculating a plaintiff's own harm. *Atl. Research Mktg. Sys., Inc. v. Troy*, No. CIV.A.07-11576-PBS, 2010 WL 1904849, at *6 (D. Mass. May 11, 2010); *see also Auto Flat Car Crushers, Inc.*, 469 Mass. at 823–24; *Shaulis*, 865 F.3d at 11. Dr. Bell could have undertaken an alternative analysis, but did not. Tr. 5-49:20 to 5-51:24.

260. In sum, Astellas has failed to meet its burden of proving it sustained any cognizable "actual damages" for purposes of its M.G.L.c. 93A, §11 claim.

261. Even if "implied value" were a proper measure of damages (it is not), Astellas has not established a nexus between the accused activity and the damages. The lynchpin of Dr. Bell's analysis was to assume – based solely on his reading of Dr. Fortier's report – that ImStem's T-MSC technology was based entirely on Astellas' HB-MSC technology. Tr. 5:53:17 to 5-63:14. He argued that ImStem's value was thus based entirely on Astellas technology.

262. Dr Bell's assumption is inconsistent with the facts. Dr. Fortier's testimony at trial was *not* that T-MSC technology was "entirely" based on HB-MSC technology; rather she stated that HB-MSCs merely "*helped* [Defendants] develop" their T-MSC technology. Tr. 3-120:24 to 3-121:2 (emphasis added); Tr. 9-33:19 to 9-34:9; Tr. 3-119:4-7 ("contributed to"); Tr. 9-30:20 to 9-32:7, Tr. 9-33:16 to 9-34:9, Tr. 9-51:17 to 9-53:5, 9-54:23 to 9-55:8.[36]

263. Further, as noted above, Defendants' development of their own technology was unrelated to Astellas' HB-MSC technology. There was nothing unfair or deceptive about the Defendants' access to the EAE model.

CONCLUSION

WHEREFORE, for the reasons set forth above, Defendants respectfully request that the Court accept their Findings of Fact and Conclusions of Law and incorporate them into a decision entering judgment in favor of the Defendants on all counts. Specifically, the Defendants ask that Drs. Xu and Wang remain on the '551 patent, that they be added to the '321 patent, Dr. Wang be added to the '956 patent, and that the Plaintiff's 93A clam be dismissed with prejudice.

[36] Even if (contrary to the facts) a portion of Defendants' T-MSC technology or business used or arose from Defendants' HB-MSC technology (it did not), Astellas' damages claim would still fail because Dr. Bell never apportioned the effect. Tr. 5-67:14 to 5-69:4; 9-29:18 to 9-30:19; 9-32:15 to 33:15; 9:50:25 to 9-51:16; Tr. 9-68:16 to 9-69:2; Tr. 9-102:2 to 9-103:15 (would need to apportion).

Dated: December 4, 2020

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CERTIFICATE OF SERVICE

I hereby certify that on December 4, 2020, I caused a true copy of the foregoing document to be served upon all counsel of record via the Court's CM/ECF electronic filing system.

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